# From HIV infection to AIDS: A dynamically induced percolation transition?

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The origin of the unusual incubation period distribution in the development of AIDS is largely unresolved. A key factor in understanding the observed distribution of latency periods, as well as the occurrence of infected individuals not developing AIDS at all, is the dynamics of the long lasting struggle between HIV and the immune system. Using a computer simulation, we study the diversification of viral genomes under mutation and the selective pressure of the immune system. In common infections vast spreading of viral genomes usually does not takes place. In the case of an HIV infection this may occur, as the virus successively weakens the immune system by depletion of $CD4^+$ cells. In a sequence space framework, this leads to a dynamically induced percolation transition, corresponding to the onset of AIDS. As a result, we obtain the prolongated shape of the incubation period distribution, as well as a finite fraction of non-progressors that do not develop AIDS, comparing well with results from recent clinical research.

It is a well known empirical fact that incubation times of most diseases obey a lognormal distribution, only varying in their distributions' mean and dispersion factors. This has been verified for many single-exposure, common vehicle epidemics and is often referred to as "Sartwell's model" [1,2]. Vice versa, this allows for estimates of exposure types as well as etiology of disease from an observed incubation period distribution [3–5]. Recently, the underlying dynamics that generate the incubation period distribution, as well as mechanisms that lead to deviations from the common distribution, have gained attention [6–8].

One of the most prominent examples for a deviation from the lognormal case is the distribution of waiting times between HIV infection (seroconversion) and the onset of AIDS, which is supported by data sets from various studies [9–14]. The divergence from lognormality, extraordinarily long incubation times, and the occurrence of non-progressors (patients not developing AIDS) suggest a more complex generating dynamics than observed in other infectious diseases. While much effort has been spent on parametric estimates of the incubation period distribution [15], we here ask which are possible mechanisms of the underlying dynamics. Any such attempt has to take into account the HIV-specific negative feedback to the host's immune system. While the immune system develops an epitope-specific answer to HIV, as it does to any other antigenic invasion, it is weakened by HIV in a way that is not common to other viral infections. HIV targets the replicative machinery of $CD4^+$ cells which are depleted when viruses proliferate. $CD4^+$ cells as T helper cells are essential actors within an immune response. Therefore HIV is able to globally weaken the host's resistance against antigens.

In earlier approaches, the onset of AIDS has been associated with the passage of an antigenic diversity threshold in the framework of differential equation models [16,17]. More recently, progress has been made to overcome the limitations of analytical models with respect to topological effects in the shape space of receptors and in physical space. Cellular automaton models have been defined and investigated that show the typical separation between the time scales of primary infection and the onset of AIDS [18,19].

In this article we take an alternative approach and combine cellular automata with a sequence space framework in order to model typical characteristics of the time course of HIV infection. In the following sections we will first define a framework to represent ordinary infections within the scope of percolation theory. From there we will extend the model to describe the special case of HIV infection and discuss the distribution of incubation periods. Numerical simulations will be complemented by a stochastic model for the origin of the variety in incubation period distributions. Finally we discuss our findings in the context of empirical data on HIV survival.

## I. PERCOLATION MODEL OF INFECTION

Along the course of an infection one generally observes a diversification of viral genomes due to mutation and the selective pressure of the immune system. This coevolutionary dynamics can be modeled within a sequence space framework [20]. Representing viral genomes by strings of length $n$, built up from an alphabet of length $\lambda$, we can describe their diversification as spread in sequence space. Analogously, let us assign a sequence to the respective immune receptor matching the viral strain. Any string in sequence space is assumed to represent a viral epitope, as well as its complementary immune receptor. Thus each sequence is characterized by a viral and an immunological state variable. A mathematical framework to describe the dynamics in such a space can be found in percolation theory [21] and in theories for epidemic spreading, i.e. SIR models [22,23]. However, while those models apply cellular automata to the interaction of organisms, we here apply the mathematical

concept to modeling the populations of immune cells and viruses within one organism. Adopting the notation of SIR models, we call a site in sequence space susceptible, if it in principle can harbor a virus. It is denoted as infected, if the system contains a virus with an epitope motif represented by the site's string. If a viral sequence meets immune response it is removed and the system is immunized against it. In this case and in case a site in principle is inaccessible for a virus, it is called recovered (or removed). Aside from this, two immunological states are distinguished. An immune receptor shape may or may not be present within the immune repertoire. We set up a system in which a site is inaccessible for viral sequences with probability $D_0$ accounting for the fact that the viral genome is not arbitrary. In addition we introduce a probability of immunological presence at any site in sequence space $\rho_{is}(t)$ with $\rho_{is}(0) = \rho_0$. This means that for sufficiently large systems the initial density of recovered sites is $R(0) = D_0 + \rho_0 - D_0\rho_0$. Taking also into account the densities of susceptible sites $S(t)$ and of infected sites $\rho_v(t)$ one obtains the relation

$$S(t) + \rho_v(t) + R(t) = 1 \qquad \forall t. \tag{1}$$

As replication of viral and immunological entities is afflicted with copy fidelities $q_v < 1$ and $q_{is} < 1$, the system shows viral - and in response immunological - spread in sequence space. Introducing some viral strains into a so far unaffected system leads to a dynamics that is modeled within the cellular automaton approach by iterating the following steps:

1. Choose a random site.
2. If the site represents an active immune receptor
   (a) mutate any bit with probability $1 - q_{is}$
   (b) if a new immunological strain is generated and the mutant matches an infected site reset the site's viral status to recovered and assign the immunological state to be positive.
3. If the site is infected
   (a) mutate any bit with probability $1 - q_v$
   (b) if a new strain is generated and corresponds to a susceptible site the site gets infected.

A viral strain generates a specific mutant strain at Hamming distance $d$ (which is the number of differing bits) with probability $\frac{(1-q_v)^d q_v^{n-d}}{(\lambda-1)^d}$ which will survive as long as it meets a susceptible site. Equally an immunological mutant strain is originated with probability $\frac{(1-q_{is})^d q_{is}^{n-d}}{(\lambda-1)^d}$ under the condition that it coincides with an infected site. Otherwise we assume that the immunological mutant is not sufficiently amplified to establish a new strain.

Such a system shows two regimes of qualitatively different behavior. Below a percolation threshold depending on the above parameters the source of infection will stay negligible in size compared to the system size, such that $R(\infty) = R(0)$ in the limit of infinite system size. Above the percolation threshold a virus will spread all over the system before it gets defeated. Accordingly $R(\infty) > R(0)$.
To determine the threshold conditions within a mean field approach ("fully mixed" approximation), we introduce the following system of differential equations

$$\begin{aligned}
\frac{dS}{dt} &= -\sum_{d=1}^{n} \binom{n}{d} (\lambda-1)^d \frac{(1-q_v)^d q_v^{n-d}}{(\lambda-1)^d} \rho_v S \\
&= -(1-q_v^n)\rho_v S \qquad (2)\\
\frac{d\rho_v}{dt} &= -(1-q_{is}^n)\rho_{is}\rho_v + (1-q_v^n)S\rho_v \qquad (3)\\
\frac{d\rho_{is}}{dt} &= (1-q_{is}^n)\rho_v\rho_{is} \qquad (4)\\
\frac{dR}{dt} &= (1-q_{is}^n)\rho_{is}\rho_v \qquad (5)
\end{aligned}$$

supplemented by the boundary conditions:

$$\begin{aligned}
S(0) &\approx 1 - R(0)\\
\rho_v(0) &\approx 0\\
\rho_{is}(0) &= \rho_0\\
R(0) &= D_0 + \rho_0 - D_0\rho_0.
\end{aligned}$$

With $(1-q_{is}^n)\rho_{is}(t) > 0$ for all $t$ and $\rho_{is}(t) = R(t) - D_0 + D_0\rho_0$ one can derive a relation between $S(t)$ and $R(t)$

$$\frac{dS}{dt} = -\frac{1-q_v^n}{1-q_{is}^n} \frac{\frac{dR}{dt}}{R - D_0 + D_0\rho_0} S$$

which yields

$$S(t) = (1 - D_0 - \rho_0 + D_0\rho_0)\left(\frac{\rho_0}{R(t) - D_0 + D_0\rho_0}\right)^{\frac{1-q_v^n}{1-q_{is}^n}} \tag{6}$$

taking into account the above boundary conditions. To evaluate conditions for the percolation threshold we can utilize

$$R_\infty = R(\infty) = 1 - S(\infty) = 1 - S_\infty$$

because in the stationary state any infected site will recover. This leads to the following relation for $R_\infty$

$$\begin{aligned}
R_\infty &= 1 - (1 - D_0 - \rho_0 + D_0\rho_0)\left(\frac{\rho_0}{R_\infty - D_0 + D_0\rho_0}\right)^{\frac{1-q_v^n}{1-q_{is}^n}}\\
&= f(R_\infty). \qquad (7)
\end{aligned}$$

It is fulfilled for $R_\infty = D_0 + \rho_0 - D_0\rho_0 = R(0)$ which means that no virus enters the system or at least cannot

gain macroscopic areas in sequence space. However, the above equation has another solution if

$$\frac{d}{dR_\infty} f(R_\infty)_{|R_\infty = R(0)} > 1,$$

because $f(R(0)) = R(0)$, $\lim_{R_\infty \to \infty} f(R_\infty) = 1$, $f(R_\infty) < 1 \quad \forall R_\infty < \infty$. Evaluating the above condition leads to the result that an invading virus can percolate in sequence space if

$$\frac{1 - q_v^n}{1 - q_{is}^n} > \frac{\rho_0}{1 - R(0)}. \tag{8}$$

It is worthwhile to consider the case $q_{is} \to 1$ which implies that the above inequality holds for any $R(0) < 1$. If the immune cells have vanishing mutation rates and accordingly lack adaptability, the virus percolates the sequence space in any case - unless immune cells occupy any site in sequence space.
For $\frac{1-q_v^n}{1-q_{is}^n} = 1$ we can explicitly determine the asymptotic density of recovered cells from the fixed point equation (7) that is solved by $R_\infty = 1 - \rho_0$ and $R_\infty = D_0 + \rho_0 - D_0\rho_0 = R(0)$. With the additional constraint that $R_\infty \geq R(0)$ one can see that $R_\infty$ decays linearly with increasing $\rho_0$ until it is equal to $R(0)$ and the subcritical regime is reached. This is confirmed by computer simulations with various sets of parameters. For the example of $D_0 = 0.5$, $q_v = q_{is} = 0.95$, $n = 15$, $\lambda = 2$ this leads to a critical immunological density $\rho_0^c = 0.32$ (the theoretical value from equation (8) is $\rho_0^c = \frac{1}{3}$).
Obviously in common infections the system is below the percolation threshold as an adequate immune response can defeat a viral attack before strains spread all over sequence space. Nonetheless it is not unreasonable to assume that the immune system operates near the percolation threshold as unnecessarily high immune receptor densities $\rho_0$ involve competitive disadvantages.

## II. PERCOLATION TRANSITION FROM HIV INFECTION TO THE ONSET OF AIDS

We are now in the position to extend our model to include HIV dynamics. An HIV model has to take care of characteristic peculiarities of HIV infections, i.e. the destruction of the immune system by the virus. We consider this by extending the algorithm of section I by the following rule: At any iteration step each viral strain is given a chance to meet a random immunological clone with probability $\rho_{is}(t)$ which thereafter is destroyed with probability $p$. If the affected site in principle is accessible for a viral strain the viral status changes back to susceptible. We initialize the system near, but below the percolation threshold, which is the natural state of a healthy immune system. As the system's qualitative behavior shows to be insensitive to the specific choice of parameters we will in the following choose the parameter settings: $D_0 = 0.5$, $\rho_0 = 0.325$, $q_v = q_{is} = 0.95$, $n = 15$, $\lambda = 2$.

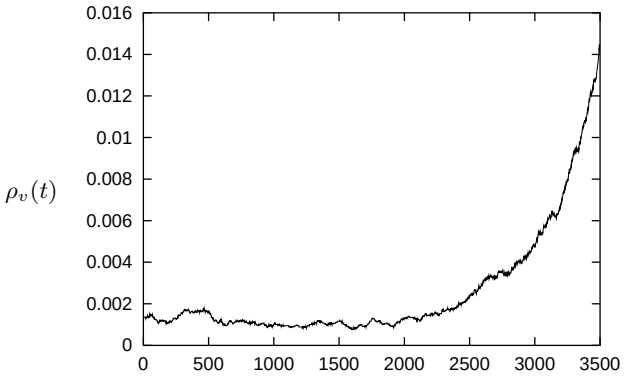


FIG. 1. Density of viral strains $\rho_v(t)$ in sequence space under evolution of the system ($D_0 = 0.5$, $\rho_0 = 0.325$, $q_v = q_{is} = 0.95$, $n = 15$, $\lambda = 2$, $p = 0.0001$).

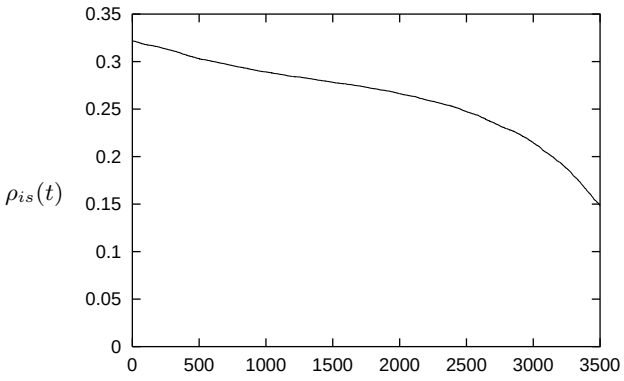


FIG. 2. Density of immunologically active sites $\rho_{is}(t)$ in sequence space ($D_0 = 0.5$, $\rho_0 = 0.325$, $q_v = q_{is} = 0.95$, $n = 15$, $\lambda = 2$, $p = 0.0001$). Note the analogy to the decline in $CD4^+$ cells under HIV infection.

Figures 1 and 2 show simulation results for $p = 0.0001$ exhibiting characteristics typical to the course of disease from HIV infection to the onset of AIDS. One observes a drift of viral epitopes due to immune pressure as found in HIV-infected individuals [24–30]. Moreover, the simulations show fluctuations in the total number of actual strains, eventually sharply increasing which corresponds to the onset of AIDS [16]. In parallel it is an empirical fact that the disease progresses with a depletion of $CD4^+$ cells [31,32,25,33] which can be assumed to be accompanied by a loss in diversity of the immune repertoire as shown in figure 2. In this picture the immune system is successively weakened while fighting the viral attack and ultimately breaks down when the virus begins to percolate in sequence space. The virus dynamically drives the

system from a subcritical regime above the percolation threshold.
It will be interesting to investigate the distribution of waiting times until percolation among systems only differing in their random initialization, which corresponds to the incubation period distribution.
To understand the generated distribution from a theoretical point of view we have to take care of the stochastic nature of $\rho_v$ as seen in figure 1. We assume that $\rho_v$ has a time dependent growth rate $r(t)$ that is superposed by noise and accordingly follows a generalized geometric Brownian motion (cp. appendix). This process $\rho_v$ has a lower absorbing boundary for $\rho_v(t) = 2^{-15}$ and converts into exponential growth after having passed an upper point of no return $\rho_v^c$. The first passage time distribution with respect to the upper boundary corresponds to the incubation period distributions under investigation. It is derived in the appendix and will be discussed in the context of simulation results and empirical HIV data in the following section.

## III. RESULTS AND DISCUSSION

We have run simulations as described in section II for various sets of parameters qualitatively leading to the same results for the time course of $\rho_v$ and $\rho_{is}$, as long as the system is initialized near but below the percolation threshold. For the following discussion let us choose the parameter settings $D_0 = 0.5$, $\rho_0 = 0.325$, $q_v = q_{is} = 0.95$, $n = 15$, $\lambda = 2$. The virgin system is infected within a ball that includes one and two bit mutants leading $\rho_v(0) = 2^{-15}(1+\binom{15}{1}+\binom{15}{2})(1-D_0-\rho_0+D_0\rho_0) \approx 0.0012$. A lower absorbing boundary of $\rho_v$ is given by $2^{-15}$ as less than one viral strain cannot exist. Further evaluation of the simulations yields estimates of $\rho_v^c = 0.002$ where the virus begins to percolate. Taking this together, we will be able to analyze the simulation results from the point of view of first passage time distributions (cp. appendix).
We have run simulations for various choices of $p$ mimicing viruses with different aggressiveness towards the immune system. For $p$ as large as 0.005 we hardly see any time period of struggle between the immune system and the virus leading to an immediate exponential growth of $\rho_v$. The system shows very short incubation periods and vanishing probability of viral defeat. The distribution of incubation periods can then be approximated by a simple inverse Gaussian distribution. Decreasing $p$ leads to longer incubation periods that correspond to periods of combat between virus and immune system as observed in figure 1.
For further discussions we will focus on simulations with $p = 0.0001$ as they show a distribution of incubation periods that are in best accordance with real data on HIV incubation periods. Nonetheless the theoretical framework as developed in the appendix will be equally applicable for arbitrary choice of $p$.
Figure 3 offers a comparison of a survival function generated by our cellular automaton model with the respective data describing the probability that a HIV positive patient has not yet developed AIDS at time $t$ after seroconversion. The HIV data are taken from a seroconverter study undertaken at the Robert Koch Institut within the CASCADE collaboration [34].

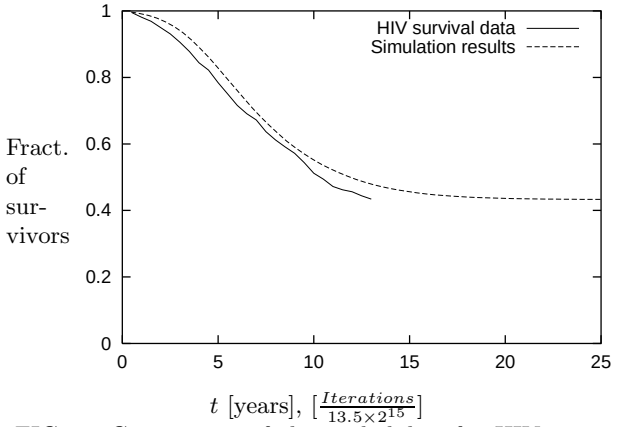


FIG. 3. Comparison of the probability for HIV positives not yet to have developed AIDS with a survival distribution generated by our simulations (after adequate renormalization of the time axis, $D_0 = 0.5$, $\rho_0 = 0.325$, $q_v = q_{is} = 0.95$, $n = 15$, $\lambda = 2$, $\rho_v(0) = 0.0012$, $\rho_v^c = 0.002$).

Figure 3 shows that the model reproduces main characteristics of the real system. The numerical simulations result in a survival function that is similar to that observed from HIV patients. In particular, they predict the occurrence of long-term survivors as observed in reality and link it to a dynamical percolation mechanism. We would like to emphasize that in this framework a quantitative comparison of our model parameters with experimental data is not very meaningful. However, any parameter setting that corresponds to a system that is initially below the percolation threshold and that is attacked with moderate aggressiveness (moderate values of $p$) will show the same qualitative behavior. This demonstrates the robustness of our model and ensures its applicability to even larger sequence spaces than those simulated here.
Furthermore let us analyze the data in the light of the first passage time distributions derived in the appendix. We have to specify the functional from of the viral growth rate $r(t)$. Different from the case of a very aggressive virus (large $p$), a constant growth rate $r(t) = \mu > 0$ does not fit the simulation results for viruses that are only moderately destructive (small $p$). Therefore let us approximate $r(t)$ underlying the simulations by an expansion in powers of $t$ as

$$r(t) = \mu + \gamma t.$$

Such a simple approach may not exactly reproduce the

waiting time distribution but can show the origin of its characteristics. This is exemplified by figure 4 where the incubation period distributions corresponding to the survival curves shown in figure 3 are approximated by a first passage time distribution with $\mu = 0.064$, $\gamma = -0.0092$ and $\sigma^2 = 0.0091$. This corresponds to the picture that the viral species initially is able to establish new strains but that its opportunities for spreading in sequence space are successively diminished. In many cases the virus nevertheless is able to percolate sequence space if its suppression takes effect too slowly. This happens in a non-deterministic manner due to stochastic fluctuations corresponding to $\sigma^2 > 0$ and generates the observed incubation period distribution.

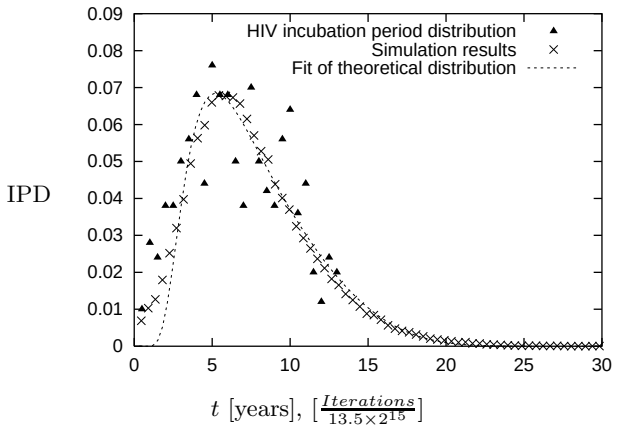


FIG. 4. Comparison of the incubation period distributions (IPD) corresponding to figure 3 with the theoretical model with $r(t) = 0.064 - 0.0092t$, $\sigma^2 = 0.0091$.

Limitations of the linear approximation become obvious with increasing $t$. $r(t)$ is unbounded for negative numbers leading to arbitrarily large destruction of viral strains with time. As a consequence, the corresponding incubation period distribution shows an unrealistic cut-off for large $t$. This disappears when considering further terms in the expansion of $r(t)$ expanding the regime of applicability of the theoretical model.

Describing the behavior of incubation periods within our model we can summarize that one observes an increase in waiting times before percolation and an enlarged fraction of cases where viral strains get totally extinct with decreasing $p$, i.e. less aggressive viral strains. This finds clear correspondence in real HIV statistics. $p$ is a measure for the vulnerability of the immune system under the attack of HIV. This virus manages its destructive penetration into T helper cells ($CD4^+$ cells) not only by membrane fusion mediated by $CD4$ but generally needs an additional co-receptor which is referred to as $CCR5$. As almost all HIV strains rely on this mechanism for replication in T cells, individuals who show a homozygous mutation leading to a non-expression of the $CCR5$ receptor have proven to be resistant against HIV infection [35]. This is well in accordance with our model which for $p = 0$ predicts that no percolation will occur. More recently it has been shown that also in individuals with heterozygous genotypes a slower progression to AIDS can be observed. Moreover those patients have a 70% reduced risk to maintain the HIV infection and develop AIDS [36]. Therefore, already a reduction of $CCR5$ receptors on $CD4^+$ cells, making viral fusion more difficult, improves the chance for prolonged or even total survival. This fits well with the predictions of the model for decrease in $p$.

Recent progress in vaccine research [37–39] further supports the model. From the model's point of view, vaccination corresponds to a local raise of immune receptors' density $\rho_0$. This drives the system far below the percolation threshold and accordingly HIV will hardly manage to spread in sequence space.

In conclusion the above HIV/AIDS phenomenology can be interpreted within our cellular automaton model. Prolonged survival as well as a finite fraction of non-progressors can be traced back to the enhanced stability below the percolation transition in this framework. Consequently, from the percolation model's point of view, vaccination and receptor blocking are encouraged as efficient strategies to overcome an HIV infection.

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## APPENDIX:

### First passage time distributions for geometric Brownian motion between two absorbing boundaries

Facing the stochastic nature of $\rho_v(t)$ we choose an ansatz in the regime before the percolation transition that expects a time dependent viral growth rate $r(t)$ of $\rho_v(t)$ which is superposed by noise. In terms of a stochastic differential equation this can be written as

$$d\rho_v(t) = r(t)\rho_v(t)dt + \rho_v(t)dB_t(0,\sigma^2) \tag{9}$$

with $B_t(0,\sigma^2)$ denoting Brownian motion with mean 0 and variance $\sigma^2 t$. Within the Stratonovich interpretation [40] this equation leads to

$$\rho_v(t) = \rho_v(0)e^{R(t)+B_t(0,\sigma^2)} \tag{10}$$

$$R(t) = \int_0^t r(t')dt'. \tag{11}$$

Accordingly $\rho_v$ is described by geometric Brownian motion that is locked between two absorbing boundaries at $2^{-n}$ (less than one strain cannot exist) and an upper critical concentration $\rho_v^c$ that leads to percolation of the virus. This can be translated to Brownian motion $B_t(R(t),\sigma^2)$

(mean $R(t)$ and variance $\sigma^2 t$) with $B_0 = 0$ and limited by

$$-a = \ln\left(\frac{2^{-n}}{\rho_v(0)}\right) < 0$$
$$b = \ln\left(\frac{\rho_v^c}{\rho_v(0)}\right) > 0.$$

The probability density $p(x,t)$ describing the distribution of the stochastic variable $B_t(R(t),\sigma^2)$ is determined by the following Fokker-Planck equation [41,42]

$$\frac{\partial p(x,t)}{\partial t} = -r(t)\frac{\partial}{\partial x}p(x,t) + \frac{\sigma^2}{2}\frac{\partial^2}{\partial x^2}p(x,t) \quad (12)$$
$$= -\frac{\partial}{\partial x}J(x,t) \quad (13)$$
$$J(x,t) = r(t)p(x,t) - \frac{\sigma^2}{2}\frac{\partial}{\partial x}p(x,t). \quad (14)$$

$J(-a,t)$ and $J(b,t)$ represent the contributions of the probability flow being absorbed at the boundaries $-a < 0$ and $b > 0$ at time $t$. In other words $J(b,t)dt$ is the probability that $B_t(R(t),\sigma^2)$ reaches $b$ for the first time in $[t, t+dt[$ under the additional condition that it has not yet met the absorbing boundary at $-a$. However, this means that $J(b,t)$ is equivalent to the first passage time distribution of the process $\rho_v(t)$ with respect to the upper boundary $\rho_v^c$, again requiring that it has not passed the lower absorbing boundary at $2^{-n}$. Note that $J(b,t)$ represents a defective probability distribution in $t$ as the upper boundary is not reached with probability 1.
Accordingly it remains to solve (12) with respect to the following initial and boundary conditions:

$$p(x,0) = \delta(x) \qquad \forall x \in [-a,b]$$
$$p(-a,t) = 0 \qquad \forall t$$
$$p(b,t) = 0 \qquad \forall t.$$

Having the reflection principle in mind one can derive a solution under this conditions as an adequate superposition of Gaussian distributions [41–43]. From this one can easily deduce using (14)

$$J(b,t) = \frac{F(a,b,\sigma^2 t)}{\sqrt{2\pi\sigma^2 t^3}} e^{-\frac{(b-R(t))^2}{2\sigma^2 t}} \quad (15)$$
$$F(a,b,\sigma^2 t) = \frac{e^{\frac{2b(a+b)}{\sigma^2 t}}\left(-a(1-e^{-\frac{2b(a+b)}{\sigma^2 t}}) + b(e^{\frac{2a(a+b)}{\sigma^2 t}} - 1)\right)}{e^{\frac{2(a+b)^2}{\sigma^2 t}} - 1}$$
$$\stackrel{a\to\infty}{\longrightarrow} b.$$

Obviously, in case of only one absorbing boundary (and $r(t) = \mu$, $R(t) = \mu t$) we get the inverse Gaussian distribution as a well known solution for this special problem [44]. A parameter setting of $D_0 = 0.5$, $\rho_0 = 0.325$, $q_v = q_{is} = 0.95$, $n = 15$, $\lambda = 2$, $\rho_v(0) = 2^{-15}(1 + \binom{15}{1} + \binom{15}{2})(1 - D_0 - \rho_0 + D_0\rho_0) \approx 0.0012$ as discussed in section III leads to $a = 3.7$ and $b = 0.51$.

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